REMARKS

Claims 11, 16-18 and 20 are pending.

The Amendment

Claim 11 is amended to clarify the claim language.

No new matter is added in the amendment. The Examiner is requested to enter the amendment and re-consider the application.

The Response

35 U.S.C. §103(a) Rejections

Claims 11, 16-18 and 20 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Warrington et al. (U.S. Publication No. 2006/0088936, published April 27, 2006) in view of Bartlett et al. (U.S. Patent No. 6,962,815, issued November 8, 2005) and further in view of Kaplitt et al. (U.S. Patent No. 6,162,796, issued December 19, 2000) and further in view of Wu Xiao (Ph.D. Dissertation 2002, University of Florida). The rejection is traversed because the references in combination do not teach or suggest all the claim elements.

1. Neither reference has disclosed double mutations at positions 484 and 585.

Although Warrington et al disclose that capsids with a single mutation at residue 484, 487, 532, 585 or 588, were partially or completely defective for heparin-agarose binding, Warrington et al do not teach or suggest the double mutation at positions of 484 and 585.

The Examiner cites [0262] of Warrington et al.: "The most severe defect was found with mutations in R585 and R588. No binding to heparin sulfate columns could be detected with either mutant (FIG. 8), and both mutations reduced the particle-to-infectivity ratio by two to three logs (Table 5). Mutants that contained substitutions at both positions had even lower infectivity." Applicants respectfully submit that the double mutations in paragraph [0262], Figure 8, and Table 5, clearly refer to position 585 and 588, and not the claimed 585 and 484. Warrington et el. describe that double mutations at position 585 and 588 reduced the infectivity, thus it does not provide a motivation for double mutation over single mutation.

The Examiner further cites another passage, "For example, R484, which is basic in all five serotypes was tested because of its proximity to R585 and R588 and subsequently proved to be involved in heparin binding." (Paragraph [0261]) This paragraph only refers to the reason why R484 (a single mutation) was identified as being involved in heparin binding. This paragraph clearly does not refer to double mutation.

At Paragraph [0075], Warrington et al. disclose that, "It was found that mutation of arginine residues at position 585 or 588 eliminated binding to heparin-agarose. Mutation of residues R484, R487, and K532 showed partial binding to heparin-agarose." This paragraph is consistent with Warrington's teaching of double mutations at positions 585 and 588. There is no suggestion in Warrington as to double mutations at positions 484 and 585, particularly Warrington et al. describe that (i) R484 only showed partial binding to heparin and (ii) the double mutations at 585/588 decreased infectivity.

2. Neither reference has disclosed the mutations at positions 484 and 585 from R to E.

In the single mutation of R484 and R585, Warrington et al. do not teach or suggest a mutation from R to E. The Examiner states that "a skilled artisan would understand that altering the amino acids of AAV capsids important for heparin binding function would require changing from the basic, Arginine, to a neutral or perhaps strongly acidic amino acid, such as Glutamic Acid (E)." Applicants respectfully do not agree.

There are more than 15 amino acids that are neutral or acidic. Without hindsight, it is not obvious to (i) select E from the 15 non-basic acids, (ii) carry out the double mutations at R484 and R585, and then (iii) prove that the R484E/R585E double-mutant "shows a similar loss of cell binding and heparin binding" and was found to be "even more affected in it infectivity than the single mutants." (Specification at page 20, lines 10-12.) There is no suggestion in any of the references that the mutation from R to E would improve the infectivity.

As the Examiner has agreed (Office Action dated 11/12/2008 at page 6), Bartlett et al., Kaplitt et al. and Wu Xiao do not teach or suggest double mutations of R484E/R585E. Therefore, Bartlett et al., Kaplitt et al. and Wu Xiao do not cure the deficiency of Warrington as to the double mutations at positions 484 and 585, particularly the change from R to E.

3. Neither reference has disclosed delivering AAV-2 vector carrying double mutations to heart muscle.

The instant application describes that the reporter gene activity of rAAV packaged into the wild-type capsid could be detected in the liver and heart muscle (Example 6, Figure 5a). However, after double-mutation at positions 484 and 585, the activity of double mutated virus was not detectable in the liver; but it was surprisingly high in the hear tissue suggesting heparin-sulfate independent transduction of heart tissue (Figure 5B).

Although Kaplitt et al. disclose the delivery of adeno-associated virus vector to heart tissue, it was not known from Kaplitt et al. whether the AAV-2 vector carrying double mutations at positions 484 and 585 would affect infectivity to heart tissue.

Unexpected Advantages of Double Mutation and Heart Tissues

As discussed above, the combination of the cited references does not include all the claim elements.

Even assuming the cited combination includes every limitation of claim 11, there is not a sufficient rationale to combine them because the results yielded by the proposed combination would not have been predictable to one of ordinary skill in the art at the time of the invention.

As described in the present application, both charge-to-alanine (R484A, R487A) and basic-to-acidic mutations (R484E, R487E) significantly reduced infectivity, cell binding and heparin binding. The R484E/R585E double-mutant "shows a similar loss of cell binding and heparin binding" and was found to be "even more affected in it infectivity than the single mutants." (Specification at page 20, lines 4-12.)

However, as shown by Example 6 (discussed above), the R484E/R585E double-mutant, when delivered to heart tissue *in vivo*, was expressed and produced a "surprisingly high" amount of protein. Because the results with the R484E/R585E double-mutant in heart tissue were unpredictable, the instant claims are not obvious over the cited references.

CONCLUSION

For all the foregoing reasons, reconsideration of and withdrawal of all outstanding rejections is respectfully requested. The Examiner is earnestly solicited to allow all claims, and pass this application to issuance.

Date: March 9, 2009

Respectfully submitted,

Viola T. Kung, Ph.D. (Reg. No. 41,131)

HOWREY LLP
2941 Fairview Park Drive, Box 7
Falls Church, VA 22042
Tel: (650) 798-3570
Fax: (650) 798-3600